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OPINION PIECE

Pneumonia Pathogenesis and the Lung Microbiome: Back to the Drawing Board

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Introduction

With the advent of microorganism identification via non-culture techniques, it is now well recognized that the upper respiratory tract as well as the lower respiratory tract of healthy individuals is normally colonized by a large number of bacteria. The recognition of the lung microbiome indicates that several aspects of our traditional model of pneumonia pathogenesis were incorrect. In this commentary, I will speculate regarding the possible mechanisms of pneumonia pathogenesis. I will also contemplate the possibility that in some patients, an episode of acute pneumonia may evolve into a chronic subclinical pneumonia.

Traditional model of pneumonia pathogenesis

Our traditional approach to the pathogenesis of pneumonia was based on the wrong assumption that the alveoli were sterile (**Figure 1.A**). In this outdated model, the first step in the development of pneumonia was the arrival of bacteria to the alveoli (**Figure 1.B**). Once bacteria arrived to the alveoli, the next step was dependent of the interaction between invading bacteria and alveolar macrophages, with two possible outcomes. Alveolar macrophages may kill the bacteria, restoring the alveolar space to the normal sterile condition, or the bacteria may overcome alveolar macrophages and multiply in the alveolar space. In response to this uncontrolled bacterial multiplication, alveolar macrophages will produce cytokines, and the local and systemic inflammatory response characteristic of pneumonia will ensue (**Figure 1.C**). In this traditional model there was a single pathway for the development of pneumonia.

The lung microbiome

At the alveolar level, the lung microbiome is constituted primarily of anaerobic organisms, with predominance of the phylum Bacteroidetes (1). Some microorganisms are living freely in the alveolar space, in a planktonic form, but half of the bacterial communities are attached to alveolar cells (2). It is likely that most of these organisms are living in cell-associated biofilm communities (**Figure 2.A**).

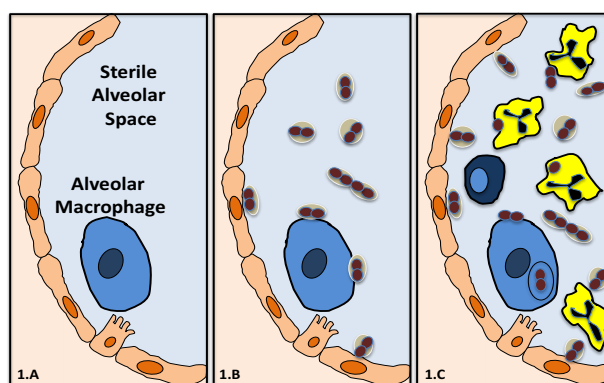


Figure 1. The sterile alveolus (**1.A**) and the traditional model of pneumonia pathogenesis with bacteria arriving and multiplying in the alveoli (**1.B**) and the development of a local inflammatory response (**1.C**).

New models of pneumonia pathogenesis

The pathogenesis of pneumonia may still involve the arrival of new bacteria into the alveolar space. Once these new bacteria arrive to the alveoli, the interaction will be among the new bacteria, the alveolar macrophages, and the alveolar microbiota. The newly arrived bacteria will need to overcome the alveolar macrophages as well as the normal alveolar flora to be able to multiply and cause pneumonia (**Figure 2.B**). If the lung microbiome is an integral part of the lung innate immunity, an abnormal alveolar microbiota, or dysbiosis, may be an important risk factor for the development of pneumonia. Prior antibiotic use may predispose to pneumonia by altering the alveolar microbiome.

As part of the pathogenesis of pneumonia, the need for the arrival of bacteria to the alveoli is no longer necessary, since bacteria, as well as viruses and fungi, are part of the normal alveolar microbiota. We can speculate that pneumonia may develop by the uncontrolled multiplication of some of the bacteria already present in the alveoli. In this model of pathogenesis, depicted in **Figure 2.C**, the etiologic agent of pneumonia will be bacteria that typically constitute the alveoli normal flora. This scenario may explain why in some patients with pneumonia an etiologic agent is not identified, since these bacteria can not be isolated using regular culture techniques.

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A final model of pathogenesis may include a combination of uncontrolled multiplication of new bacteria arriving to the alveoli associated to uncontrolled multiplication of some of the species present in the alveolar microbiota (Figure 2.D). In this type of pathogenesis, the etiology of pneumonia will be polymicrobial, with a combination of invading bacteria plus bacteria normally present in the alveoli.

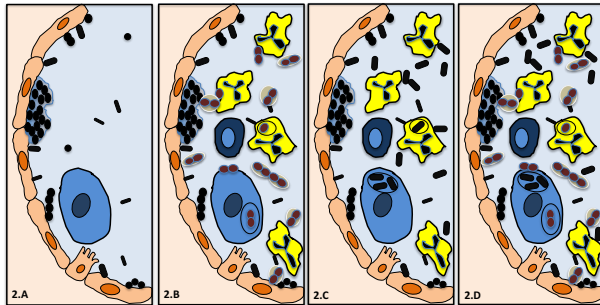


Figure 2. The lung microbiome (2.A) and three possible models for pneumonia pathogenesis (2.B, 2.C, and 2.D).

A new respiratory infection: Chronic subclinical pneumonia

Persistent subclinical inflammation has been documented in some patients after clinical resolution of an episode of community-acquired pneumonia (3). These patients are at increased risk for cardiovascular events, rehospitalization, and mortality. The reason for this persistent lung inflammation is not clear. It can be speculated that current antibiotic therapy for pneumonia is able to kill invading microorganisms, but an abnormal alveolar microbiota may persist even after the patient is clinically cured. The persistent multiplication of some species belonging to the alveolar microbiota will set the stage for a subclinical respiratory infection associated to low level chronic lung inflammation, an entity that can be defined as chronic subclinical pneumonia. This unregulated lung inflammation may persist until the normal alveolar bacteria composition is restored. Therapeutic interventions aimed to restore homeostasis of the lung microbiome may be necessary to curtail chronic lung inflammation after an episode of pneumonia.

Conclusion

From all the ideas expressed in this opinion piece, we can be certain that our traditional model of pneumonia pathogenesis is incorrect. All other concepts regarding the role of the lung microbiome in the pathogenesis of acute pneumonia or the development of chronic subclinical pneumonia are only hypothesis that will need to be tested with further research. The lung microbiome has forced all investigators in the field of pneumonia to go back to the drawing board.

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